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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
|-----------------|-------------|----------------------|---------------------|
| 09/419,328      | 10/15/99    | ROOK                 | A PENN-0701         |

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HM12/0314

EXAMINER

JIANG, D

| ART UNIT | PAPER NUMBER |
|----------|--------------|
| 1646     | 7            |

DATE MAILED: 03/14/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

|                              |                        |                     |
|------------------------------|------------------------|---------------------|
| <b>Office Action Summary</b> | <b>Application No.</b> | <b>Applicant(s)</b> |
|                              | 09/419,328             | ROOK, ALAIN H.      |
|                              | <b>Examiner</b>        | <b>Art Unit</b>     |
|                              | Dong Jiang             | 1646                |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 12/28/00.
- 2a) This action is FINAL.                    2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 1-3 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 1-3 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claims \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.
- 11) The proposed drawing correction filed on \_\_\_\_\_ is: a) approved b) disapproved.
- 12) The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. § 119

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some \* c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

#### Attachment(s)

- 15) Notice of References Cited (PTO-892)
- 16) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_
- 18) Interview Summary (PTO-413) Paper No(s) \_\_\_\_\_
- 19) Notice of Informal Patent Application (PTO-152)
- 20) Other: \_\_\_\_\_

**DETAILED OFFICE ACTION**

Claims 1-3 remain under consideration. Claim 3 has been amended as in paper number 6, filed on 28 December, 2000. The new amendment has been entered.

**Withdrawal of Objections and Rejections:**

Applicant's arguments with respect to the rejections of claims 1-3 under 35 U.S.C. 102(b) and 103(a) have been considered but are moot in view of the new ground(s) of rejection.

The rejection of claim 3 under 35 U.S.C. 103(a) as being unpatentable over Rook et al. (1996) is withdrawn in view of applicant's amendments.

**Rejections Over Prior Art:**

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as being unpatentable over Rook et al. (Clin Exp Immunol, 1997 January, 107 Suppl 1: 16-20, provided by the applicant).

Rook et al. disclose phase I/II clinical trials of recombinant IL-12 for treatment of cutaneous T cell lymphoma (CTCL), wherein IL-12 is administered subcutaneously (page 18, lines 18-20).

Rook et al. does not explicitly teach a pharmaceutically acceptable carrier with IL-12 in above method.

However, it is well known in the art that a purified protein agent is usually used in combination with other agent(s) (such as dissolving solutions) rather than used as its crystal form alone. The fact that recombinant IL-12 is administered subcutaneously in Rook's method indicates the protein is dissolved. Dissolving solutions, such as water or buffers, can be "a pharmaceutically acceptable carrier". Therefore, Rook's method anticipates the claim.

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Claim 3 is rejected under 35 U.S.C. 102(a) as being anticipated by Lee et al. (Leukemia and Lymphoma, 1998 May, 29(5-6):427-38).

Lee et al. teach a composition comprising recombinant IL-12 and IL-15, and demonstrate the synergistic effects of the combination of IL-12 and IL-15 with regard to anti-tumor immunity (page 432, the last paragraph, and Figure 3).

Instant claim 3 is drawn to a composition comprising recombinant IL-12 and a retinoid, IL-15, IL-18, IFN- $\alpha$  or IFN- $\gamma$ . Lee's composition comprises IL-12 and IL-15. Even though IL-12 plus IL-15-induced IFN- $\gamma$  production was not assessed in the reference, stimulation of IFN- $\gamma$  production by such composition would be an inherent feature of the same compositions. Therefore, the cited reference clearly anticipates the instant claim. With respect to the claim limitation that said composition is for treatment of advanced cutaneous T cell lymphoma, it is an intended use of the claimed composition, and does not alter the nature of the composition. Accordingly, the claimed composition is anticipated by that of Lee et al..

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rook et al. (Ann NY Acad, 1996, 795:310-318, provided by the applicant), in view of Verbik et al. (Clin Exp Metastasis, 1996, 14:219-229, provided by the applicant).

Rook et al. report studies in Sezaay syndrom (SzS), an advanced form of CTCL characterized with typical findings in a marked depressed IFN- $\gamma$  production (Th1 cytokine) and excess IL-4 and IL-5 production (Th2 cytokines) by PBMCs, and other immune abnormalities (abstract). Further, the cited reference discloses that PBMCs from patients with SzS exhibit a marked defect in IL-12 production (Figure 1), which is a potent stimulus for IFN- $\gamma$  production. By addition of recombinant IL-12 to PBMCs from SzS patients, Rook et al. demonstrate that depressed IFN- $\gamma$  production is normalized in vitro (Figure 2), indicating a marked defect in IL-12

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production by SzS PBMCS may be an important factor in the failure of producing normal amounts of IFN- $\gamma$  and mediating normal cell-mediated immunity. Rook et al. clearly suggest that "the implications of possibly restoring nearer normal levels, through the provision of exogenous recombinant IL-12, ... are substantial" (page 315, the second paragraph), "the presence of normal *in vivo* concentrations of both IL-12 and IFN- $\gamma$  could favor the enhancement of anti-tumor cell-mediated immune responses that are deficient in this disorder" (page 316, the first paragraph), and "in view of the specific immune defects in ..., institution of controlled trials using recombinant IL-12 alone and with other Th1-inducing agents should be pursued" (page 316, the third paragraph).

Rook et al. does not teach a method for *in vivo* treatment.

Verbik et al. teach a method for treatment of a murine lymphoma with IL-12 in mice. The therapeutic effect of IL-12 was demonstrated by a very significant increase in the overall survival of the treated animals (Figure 1).

Verbik et al. does not teach the therapeutic application of IL-12 in advanced cutaneous T cell lymphoma (CTCL) in human.

With respect to claim 1, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to design a method for treatment of advanced CTCL in a human by administering recombinant IL-12 based upon strong indications taught by Rook (IL-12 deficiency and normalization of IFN- $\gamma$  by exogenous IL-12 in SzS PBMCS). One of ordinary skill in the art would have been motivated to do so as Verbik et al. teach strongly toward an expectation of success at treating a lymphoma *in vivo*.

Therefore, the art taken as a whole provides motivation to treat an advanced CTCL in a human by administering recombinant IL-12 as suggested by Rook et al. with a reasonable expectation that recombinant IL-12 regimen would be beneficial to these patients as indicated by Verbik's *in vivo* results.

With respect to claim 2, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to design a method as claimed for treatment of advanced CTCL in a human by administering recombinant IL-12 *with* an adjunct therapeutic agent stimulating IFN- $\gamma$  production, based upon strong indications taught by Rook, as IFN- $\gamma$  is a Th1

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cytokine. One of ordinary skill in the art would have been motivated to do so at Rook's suggestion and reasonably would have expected success because both IL-12 and an IFN- $\gamma$  inducing agent share a same function towards stimulating IFN- $\gamma$  production.

Therefore, the art taken as a whole provides motivation to treat an advanced CTCL in a human by administering recombinant IL-12 with an adjunct therapeutic agent stimulating IFN- $\gamma$  production as suggested by Rook et al. with a reasonable expectation that such combination therapy would be beneficial to these patients because of the functional similarity of the two agents.

With respect to claim 3, a composition comprising recombinant IL-12 and a retinoid or IFN- $\gamma$  is obvious over the same reference for the following reasons: Rook et al. clearly state that "the presence of normal *in vivo* concentrations of *both* IL-12 and IFN- $\gamma$  could favor the enhancement of anti-tumor cell-mediated immune responses that are deficient in this disorder". Further, Rook et al. clearly suggest a method for treating CTCL using recombinant IL-12 with other Th1-inducing agents (see above), and IFN- $\gamma$  is a Th1 cytokine. Additionally, the cited reference discloses that "retinoids appear to produce effects on IFN- $\gamma$  production" (page 316, the second paragraph).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to make a composition comprising recombinant IL-12 and IFN- $\gamma$  or a retinoid in order to practice the method for treatment of advanced CTCL "using recombinant IL-12 ... with other Th1-inducing agents" suggested by Rook et al.. One of ordinary skill in the art would have been motivated to do so as clearly suggested by Rook et al. and reasonably would have expected success for the same reason addressed above (in claim 2 rejection).

Claim 3 is further rejected under 35 U.S.C. 103(a) as being unpatentable over Rook et al. (1996) and Verbik et al. as applied to claims 1-3 above, and further in view of Osaki et al. (J. Immunol., 1998 February, 160: 1742-49), and Rook et al. (Clin Exp Immunol, 1997, 107 Suppl 1: 16-20, provided by the applicant).

Rook et al. (1996) does not teach a composition comprising recombinant IL-12 and IL-18, or IFN- $\alpha$  specifically.

Osaki et al. teach a composition comprising murine recombinant IL-12 and IL-18 (another IFN- $\gamma$  stimulus), and a method of treating a murine fibrosarcoma *in vivo* using said composition. Osaki et al. demonstrate additive antitumor effects of the combination treatment with IL-12 and IL-18, and increased level of serum IFN- $\gamma$  *in vivo* with such treatment (page 1743, right column, the last two paragraphs, Figure 2 and 3, and page 1748, left column, the second paragraph).

Rook et al. (1997) teach that IFN- $\alpha$  potently suppresses the abnormal IL-4 and IL-5 production (as mentioned above, SzS PBMCs produce excess amount IL-4 and IL-5), and IL-12 appears to exert a small, but consistent inhibitory effect on the excess IL-4. Moreover, this inhibitory effect of IL-12 appears to be additive with the inhibitory effect of IFN- $\alpha$  (page 17, the first and the last paragraphs).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to make a composition comprising recombinant IL-12 and IL-18 or IFN- $\alpha$  taught by Osaki et al. or suggested by Rook et al. (1997) in order to treat advanced CTCL as suggested by Rook's (1996 and 1997). One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success as both Osaki and Rook (1997) teach strongly the additive effects of the combination treatment with IL-12 and IL-18 or IFN- $\alpha$ .

Advisory Information:

No claim is allowed.

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 703-305-1345. The examiner can normally be reached on Monday - Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for the organization where this application or proceeding is assigned is 703-308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.



LORRAINE SPECTOR  
PRIMARY EXAMINER

DJ  
3/7/01